9; page 17, lines 12-17; SEQ ID NOs: 1, 4; page 28, line 6 to page 30, line 37; page 11, line 28 to page 12, line 12; page 3, Table 1; page 15, lines 12-14; page 25, lines 11-25; and Figures 2D, 3B, 3C, 4B, 7A, 7B, 7C, 7F, 7G, 9, and 11B. Support new claims 122-124 may be found *inter alia* in the specification as originally filed at page 13, lines 14-37, and page 16, line 10 to page 17, line 4. Support new claims 125-127 may be found *inter alia* in the specification as originally filed at page 14, lines 1-5. Support new claims 128-131 may be found *inter alia* in the specification as originally filed at page 14, lines 26-31. Support new claim 132-136 may be found *inter alia* in the specification as originally filed at page 15, lines 1-2 and 12-14. Support new claim 137-138 may be found *inter alia* in the specification as originally filed at page 3, Table 1. Support new claim 139 may be found *inter alia* in the specification as originally filed at page 15, line 26 to page 16, line 9; page 28, line 6 to page 30, line 37; page 11, line 28 to page 12, line 12; page 25, lines 11-25; and Figures 2D, 3B, 3C, 4B, 7A, 7B, 7C, 7F, 7G, 9, and 11B. Support new claims 140-141 may be found *inter alia* in the specification as originally filed at page 15, lines 23-24.

Accordingly, applicants respectfully request that the Amendment be entered.

Compliance with Sequence Rules

On page 2 of the October 31, 2001 Office Action, the Examiner objected to claims 27, 50, 52, and 75 for reciting an amino acid sequence that is not identified by a sequence identifier. The Examiner required that applicants amend the claims to include sequence identifiers. A copy of the Notice to Comply With Sequence Rules is attached hereto as **Exhibit 1**.

In response, applicants have canceled claims 27-76 and added new claims 121-141. New claims 121 and 140 include sequence identifiers for the recited sequences. Accordingly, applicants respectfully request that Examiner withdraw this ground of objection.

Rejection under 35 U.S.C. §112, second paragraph

On page 3 of the October 31, 2001 Office Action, the Examiner rejected claims 27-37, 40-46, 50-62, 65-70, 75 and 76 under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. The Examiner alleged that claims 27 and 52 are indefinite because the claims recite detecting either a displaced protein or detecting a complex. The Examiner alleged, however, that there is no indication in the claims what the purpose is of detection of a complex.

In response, in order to expedite the prosecution of the subject application, but without conceding the correctness of the Examiner's position, applicants have canceled claims 27-76 and added new claims 121-141. New independent claim 121 recites:

121. A method of identifying a compound that inhibits specific binding between a signal-transducing protein and a cytoplasmic protein containing the amino acid sequence (G/S/A/E)-L-G-(F/I/L) (SEQ ID NO: 1), wherein each - represents a peptide bond, each parenthesis encloses amino acids which are alternatives to one other, and each slash within such parentheses separates the alternative amino acids, which comprises:

(a) contacting the cytoplasmic protein bound to the signal-transducing protein with a plurality of compounds under conditions permitting binding between a known compound previously shown to be able to (A)(i) displace the signal-transducing protein bound to the cytoplasmic protein and (ii) form a complex with the cytoplasmic protein to which the signal-transducing protein is no longer bound, or (B)(i) displace the cytoplasmic protein bound to the signal-transducing protein and (ii) form a complex with the signal-transducing protein to which the cytoplasmic protein is no longer bound; and

(b) detecting the displaced signal-transducing protein or the complex from step (a)(A), or the displaced cytoplasmic protein or the complex from step (a)(B), wherein the presence of any of the displaced signal-transducing protein, the displaced cytoplasmic protein, the complex between the compound and the cytoplasmic protein, or the complex between the compound and the signal-transducing protein indicates that the compound inhibits specific binding between the signal-transducing protein and the cytoplasmic protein;

wherein the signal-transducing protein is a CD4 receptor, a p75 receptor, a serotonin 2A receptor, a serotonin 2B receptor, a NMDA receptor, or a K^+ channel; or is a peptide consisting essentially of 3-13 amino acids having at its carboxyl terminus the amino acid sequence (S/T)-X-(V/I/L) (SEQ ID NO: 4), wherein each - represents a peptide bond, each parenthesis encloses amino acids which are alternatives to one other, each slash within such parentheses separates the alternative amino acids, and the X represents any amino acid which is selected from the group comprising the twenty naturally occurring amino acids.

Applicants maintain that new claim 121 clearly points out that detecting the complex is one method of determining that the compound inhibits specific binding between the signal-transducing protein and the cytoplasmic protein.

In view of the foregoing amendments and remarks, applicants respectfully request that Examiner withdraw this ground of rejection.

Rejection under 35 U.S.C. §112, first paragraph

On page 3 of the October 31, 2001 Office Action, the Examiner rejected claims 27-37, 43-46, 50, 51, 52-62, 68-70, 75 and 76 under 35 U.S.C. §112, first paragraph, because the specification, while being enabling for how to use methods of screening for compounds that disrupt the association between Fas and FAP, allegedly does not reasonably provide enablement for how to use methods of screening for compounds that disrupt the association between any cytoplasmic protein and signal transducing protein. The Examiner alleged that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The Examiner stated that factors to be considered in determining whether undue experimentation would be required to practice the full scope of the claimed inventions are: 1) quantity of experimentation necessary; 2) the amount of direction or guidance presented in the specification; 3) the presence or absence of working examples; 4) the nature of the invention; 5) the state of the prior art; 6) the relative skill of those in the art; 7) the

predictability or unpredictability of the art; and 8) the breadth of the claims. See Ex parte Forman, 230 USPQ 546, BPAI, 1986.

The Examiner alleged that the claims are broadly drawn to screening methods for the screening of compounds that disrupt the association between a cytoplasmic protein and a signal-transducing protein. The Examiner also alleged that the specification confines its teachings to how to screen for compounds that disrupt the binding of Fas with FAP. The Examiner alleged that the prior art also teaches such methods, and also teaches that the use of such screening methods is to discover agents that may be used to modulate apoptosis. The Examiner stated that the basis for this teaching is that the prior art demonstrates that the association between Fas and FAP is a step that is required in signaling of apoptosis (see Reed et al, U.S. Patent 5,876,939, col. 29, line 10 - col. 30, line 47). The Examiner alleged that the instant specification fails to teach how to use screening methods for all of the possible combinations of cytoplasmic protein and signal-transducing protein because the specification fails to teach the biological significance of any other combination, other than that of Fas with FAP. Thus, the Examiner concluded, the specification appears to provide an invitation to research to discover uses of the most of the claimed screening assays, and therefore, it would require undue experimentation to first establish the biological significance of the association between a cytoplasmic protein and a signal-transducing protein, and then to use this information to know how to use the full scope of the claimed methods.

In response, in order to expedite the prosecution of the subject application, but without conceding the correctness of the Examiner's position, applicants have canceled claims 27-76 as

indicated above. Applicants note that new claims 121-141 are not directed to methods for screening compounds that disrupt the association between all cytoplasmic proteins and all signal-transducing proteins. Rather, new independent claim 121 is directed to a method of identifying a compound that inhibits specific binding between a signal-transducing protein and a cytoplasmic protein, wherein the cytoplasmic protein contains the specific amino acid sequence (G/S/A/E)-L-G-(F/I/L) and wherein the signal-transducing protein is a CD4 receptor, a p75 receptor, a serotonin 2A receptor, a serotonin 2B receptor, a NMDA receptor, or a K^+ channel; or is a peptide consisting essentially of 3-13 amino acids having at its carboxyl terminus the specific amino acid sequence (S/T)-X-(V/I/L).

Furthermore, the specification does not confine its teachings to how to screen for compounds that disrupt the binding of Fas with FAP. The specification also provides detailed examples for the binding between FAP and p75 low-affinity nerve growth factor receptor (NGFR). See page 32, lines 1-30; page 9, lines 1-35; and Figures 8-12. In addition, TABLE 1, page 3, teaches examples of protein-protein interactions involving PDZ domains, including those involving the NMDA receptor and a K+ channel, which are signal transducing proteins. The specification also teaches additional signal transducing proteins that comprise the specific (S/T)-X-(V/I/L) binding motif, e.g. human CD4 receptor (Figure 7B), human colorectal mutant cancer protein (Figure 7D), protein kinase C, alpha type (Figure 7E), serotonin 2A receptor (Figure 7F), serotonin 2B receptor (Figure 7G), and adenomatosis polyposis coli tumor suppressor protein (Figure 7H) (page 15, lines 12-21).

Furthermore, the specification does teach the biological significance of combinations other than that of Fas with FAP. The significance of the interaction between FAP and p75NGFR is discussed on page 32, lines 15-30. Furthermore, applicants maintain that, prior to the July 22, 1996 priority date of the subject application, the skilled artisan would have known the importance of p75NGFR in inducing apoptosis as evidenced by Rabizadeh et al. (1993) (Induction of apoptosis by the low-affinity NGF receptor. Science 261: 345-8) and Rabizadeh et al. (1994) (Expression of the low-affinity nerve growth factor receptor enhances β-amyloid peptide toxicity. PNAS 91: 10703-6), copies of which are attached hereto as **Exhibits A and B**, respectively.

Accordingly, applicants maintain that the teachings of the specification enable the skilled artisan to practice the claimed invention. In view of the foregoing amendments and remarks, applicants respectfully request that the Examiner reconsider and withdraw this ground of rejection.

Rejection under 35 U.S.C. §102(e)

On page 5 of the October 31, 2001 Office Action, the Examiner rejected claims 27-37, 40-42, 50-62, 65-67, 75, and 76 under 35 U.S.C. §102(e) as allegedly anticipated by Reed and Sato (U.S. Patent 5,876,939; issued March 2, 1999; effective U.S. filing date March 27, 1995). The Examiner stated that Reed discloses methods for screening for compounds that disrupt the binding of Fas (a signal transducing protein that is a receptor) with FAP (a cytoplasmic protein) (see column 13, line 51- column 14, line 6; and column 14, lines 18-20). The Examiner stated that the screening assay may be performed by a yeast two hybrid assay or by assaying the level of a reporter gene (column 15, lines 13-

27) and that the assay may be adapted for use in mammalian cells (column 15, lines 42-47). The Examiner stated that the compounds that may be screened are peptides, peptidomimetics, inorganic compounds, and organic compounds (see column 13, lines 62-65). The Examiner stated that Reed discloses that Fas is expressed in breast, colon, and prostate cells (see column 1, lines 44-47) and that it is well known in the art that Fas is expressed in T-cells. The Examiner concluded that Reed discloses methods of screening that are that claimed.

In response, in order to expedite the prosecution of the subject application, applicants have canceled claims 27-76 and added new claims 121-141 as described above. Applicants maintain that new claims 121-141 are not directed to screening methods that involve Fas and accordingly that new claims 121-141 are not anticipated by Reed and Sato (U.S. Patent No. 5,876,939).

Accordingly, in view of the foregoing amendments and remarks, applicants respectfully request that the Examiner reconsider and withdraw this ground of rejection.

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

This Supplemental Information Disclosure Statement is submitted under 37 C.F.R. §1.97(c)(2) to supplement the Information Disclosure Statement filed on April 12, 1999.

According to 37 C.F.R. §1.97(c), an Information Disclosure Statement shall be considered by the U.S. Patent and Trademark Office if filed before the mailing date of any of a Final Office Action under 37 C.F.R. §1.113, a Notice of Allowance under 37 C.F.R. §1.311, or an action that otherwise closed prosecution in

the application, and if the Statement is accompanied by the fee as set forth in C.F.R. §1.17(p). Applicants are filing this Supplemental Information Disclosure Statement before the issuance of a Final Office Action, a Notice of Allowance, or an action closing prosecution in the subject application. The fee set forth in C.F.R. §1.17(p) for submission of an Information Disclosure Statement is ONE HUNDRED EIGHTY DOLLARS ($180.00), and a check including this amount is enclosed.

In accordance with their duty of disclosure under 37 C.F.R. §1.56, applicants would like to direct the Examiner's attention to the following reference which is listed on the attached Form PTO-1449 (**Exhibit 2**) and attached hereto as **Exhibit 3**:

U.S. Patent No. 5,747,245, issued May 5, 1998, Reed and Sato.

In accordance with their duty of disclosure under 37 C.F.R. §1.56, applicants would like to direct the Examiner's attention to the following references which are listed on the attached Form PTO-1449 (**Exhibit 2**). These references were previously submitted or cited in connection with the prosecution of U.S. Serial No. 08/681,219. The subject application claims priority of the filing date of U.S. Serial No. 08/681,219 under 35 U.S.C. §120. According to 37 C.F.R. §1.98(d), copies of patents or publications that were previously cited by, or submitted to, the Patent Office in connection with such prior applications need not accompany the Information Disclosure Statement. Accordingly, copies of the following references are not attached to this Information Disclosure Statement:

1. U.S. Patent No. 5,783,666, issued July 31, 1998, Albertsen et al.;

2. PCT International Publication No. WO 95/34661, published December 21, 1995;

3. PCT International Publication No. WO 97/11091, published March 27, 1997;

4. Desjardins, P. and Morais, R. Sequence and gene organization of the chicken mitochondrial genome. A novel gene order in higher vertebrates. J. Mol. Biol. 212: 599-634, 1990;

5. Niethammer et al. Interaction between the C terminus of NMDA receptor subunits and multiple members of the PSD-95 family of membrane-associated guanylate kinases. J. Neurosci. 16(7): 2157-63, 1996;

6. Okimoto, R. et al. The mitochonodrial genomes of two nematodes, Caenorhabditis elegans and Ascaris suum. Genetics 130: 471-498, 1992;

7. Pal, D. and Chakrabarti, P. Estimates of the loss of main-chain conformational entropy of different residues on protein folding. Proteins: Structure, Function, and Genetics 36: 332-339, 1999; and

8. Parker, W. and Stezowski, J.J. The surface of -sheet proteins contains amphiphilic regions which may provide

clues about protein folding. Proteins: Structure, Function, and Genetics 25: 253-260, 1996.

PCT International Publications Nos. WO 95/34661 and WO 97/11091 were cited in a Supplementary Partial European Search Report issued January 14, 2002 in connection with corresponding European Patent Application No. 97937999.7. A copy of the Supplementary Partial European Search Report is attached hereto as **Exhibit 4.**

In summary, in view of the amendments and remarks made hereinabove, applicants respectfully request that the Examiner reconsider and withdraw the grounds of objection and rejection set forth in the October 31, 2001 Office Action and allow all claims now pending in the subject application, namely claims 121-141.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

No fee, other than the enclosed $640.00 fee ($460.00 for a three month extension of time plus $180.00 for submission of an Information Disclosure Statement), is deemed necessary in connection with the filing of this Amendment and Supplement Information Disclosure Statement. However, if any other fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,

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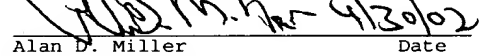
I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231.



4/30/02

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